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COMBINED DIAGNOSTICS OF PRIMARY LUNG CANCERS WITH IMMUNOLOGY EXAMINATIONS

[КОМПЛЕКСНАЯ ДИАГНОСТИКА ПЕРВИЧНОГО РАКА ЛЕГКОГО С ИСПОЛЬЗОВАНИЕМ ИММУНОЛОГИЧЕСКИХ ИССЛЕДОВАНИЙ]

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COMBINED DIAGNOSTICS OF PRIMARY LUNG CANCERS WITH IMMUNOLOGY EXAMINATIONS

RECENT TRENDS ARE TOWARDS THE LUNG CANCERS (LC) TO BECOME ONE OF THE MOST FREQUENT MALIGNANT TUMORS. BOTH STEADY RISE IN THE NUMBER OF CASES AND CANCER MORTALITY FOR THE ABOVE CANCER LOCALIZATION HAVE BEEN OBSERVED IN ALL DEVELOPED COUNTRIES [15]. AS TO RUSSIA, LUNG CANCERS ARE RANKING FIRST BOTH IN THE GENERAL PATTERN OF CANCER MORBIDITY AND ALSO AMONG THE NUMBER OF MALIGNANT TUMORS TOTAL IN MALE PATIENTS [7].

IT IS OBVIOUS THAT SUCCESSFUL TREATMENT OF LCS DEPENDS FROM THEIR DIAGNOSTICS CONSIDERABLY. TO ILLUSTRATE, THE FIVE-YEAR SURVIVAL RATE IN THE T1N0M0 STAGE PATIENTS AFTER RADICAL CURE IS CLOSE TO 70 - 85 %; FOR THE STAGE III LUNG CANCER PATIENTS, HOWEVER, THIS RATE IS NO MORE THAN 15 - 20 % [10, 17]. MOST OF THE PATIENTS, HOWEVER, ARE ADMITTED TO OUR CLINICS AT STAGES III OR IV OF THE DISEASE, AND RADICAL CURE IS ONLY POSSIBLE FOR 20 % OF SUCH PATIENTS [5, 11].

DIAGNOSTICS OF LCS IS BASED ON THE COMPREHENSIVE EXAMINATIONS OF PATIENTS TAKING DUE ACCOUNT OF THEIR MEDICAL HISTORIES, CLINICAL SYMPTOMS, AND DATA OF SPECIAL MEDICAL EXAMINATIONS. THE DIFFERENTIAL DIAGNOSTIC PROCEDURES, AS A RULE, ARE APPLIED TO THE PATIENTS HAVING PROTRACTED PNEUMONIAS, CHRONIC NONSPECIFIC

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[1] Numbers in the margins indicate pagination in the foreign text.

LUNG DISEASES (CNLD), TUBERCULOSES, AND BENIGN TUMORS. SIMILAR CLINICAL AND RADIOLOGICAL SIGNS OF DIFFERENT LUNG DISORDERS, AND ALSO CERTAIN PROBLEMS WITH DIFFERENTIAL DIAGNOSTICS ARE THE MAJOR REASONS FOR MISTAKES AND LATE DETECTION OF LCS [4].

THE TIMELY DETECTION OF LUNG CANCERS MAY BE IMPROVED BASED ON COMBINED APPLICATION OF THE UP-TO-DATE EXAMINATION PROCEDURES FOR LUNG DISORDERS [3]. NOTWITHSTANDING SOMEWHAT CONTROVERSIAL FINDINGS, ATTENTION OF THE CLINICIANS IS GETTING ATTRACTED TO THE DATA OF IMMUNOLOGY TESTS AND TUMOR MARKERS FOR DIAGNOSIS AND MONITORING OF THE LC PATIENTS [9, 18].

THE OBJECTIVE OF THIS EXPERIMENTAL RESEARCH WAS TO JUSTIFY THE OPPORTUNITIES TO IMPROVE THE EFFICIENCY OF COMBINED PRIMARY LC DIAGNOSTICS BASED ON IMMUNOLOGY EXAMINATIONS.

MATERIAL AND PROCEDURES

THE COMPARATIVE ANALYSIS OF THE INFORMATION SIGNIFICANCE OF DIAGNOSTIC PROCEDURES WAS COMPLETED IN 256 DIFFERENT-TYPE LUNG DISEASE PATIENTS ADMITTED TO THE CLINIC DUE TO SUSPICIONS OF LUNG CANCERS. AFTER OUR COMBINED EXAMINATIONS 187 PATIENTS WERE DIAGNOSED AS HAVING PRIMARY LUNG CANCERS (LC); BENIGN LUNG TUMORS (BLT) WERE FOUND IN 16 CASES, AND CNLD IN 53 CASES. AGE OF THE PATIENTS RANGED FROM 30 TO 68 YEARS.

WE HAVE EXAMINED 169 MALE AND 18 FEMALE PATIENTS, 187 IN TOTAL; AVERAGE AGE WAS EQUAL TO 55.5 YEARS. OUR ASSESSMENTS OF LUNG CANCER STAGES AND THE

EXTENT OF PRIMARY TUMORS WERE BASED ON THE INTERNATIONAL TMN CLASSIFICATION (1989). STAGE I WAS DIAGNOSED FOR 37 PATIENTS; STAGE II WAS FOUND IN 54; STAGE III - 69, AND STAGE IV IN 28 CASES. PERIPHERAL CANCERS AND CENTRAL CANCERS WERE DIAGNOSED FOR 78 (41.7 %) AND 109 (58.3 %) PATIENTS, RESPECTIVELY. SQUAMOUS CELL CARCONOMA WAS FOUND TO BE THE MAJOR HISTOLOGICAL STRUCTURE OF TUMORS (63.1 %); ADENOCARCINOMA WAS DIAGNOSED FOR 19.8 %, AND SMALL CELL CARCINOMA IN 17.1 % OF ALL CASES. WITHIN THE LC GROUP 95 PATIENTS (50.8 %) HAD CHRONIC BRONCHITIS; 21 (11.2 %) - PULMONARY FIBROSIS, AND 15 (8 %) - PULMONARY EMPHYSEMA. THE COMBINATION OF CANCER AND PULMONARY TUBERCULOSIS WAS FOUND IN 9 PATIENTS (4.8 %). THE SECOND GROUP OF ASSOCIATED ILLNESSES (CORONARY HEART DISEASE AND ESSENTIAL HYPERTENSION) FOR FOUND FOR 83 PATIENTS (44.4 %). ONLY 22 PATIENTS (11.8 %) HAD NO ANY ASSOCIATED ILLNESSES.

MALE PATIENTS, AGED 47.6 ON THE AVERAGE, DOMINATED THE GROUP OF CNLD PATIENTS (45 OF 53 IN TOTAL). THE GROUP OF BLT PATIENTS, AGED 46.3 ON THE AVERAGE CONSISTED OF 14 MALES AND 2 FEMALES. MOST OF THE LC PATIENTS (172 OR 92 %) WERE SMOKERS (AS OF THE DATE OF EXAMINATION; 10 CIGARETTES A DAY OR MORE). IN THE CNLD AND BLT GROUPS SMOKED 40 (75.5 %) AND & (43.8 %) OF PATIENTS, RESPECTIVELY.

THE PRINCIPAL DIAGNOSTIC PROCEDURES IN OUR RESEARCH INCLUDED CLINICAL/X-RAY IMAGING AND ENDOSCOPY, CYTOLOGY OF SPUTUM, TRANSTHORACIC PUNCTURES, AND MULTIFACTOR IMMUNOLOGY TESTING.

All immunology tests were completed at patients' admission for inpatient treatment. Examinations included determination of absolute content and proportions for T-lymphocytes [14] and B-lymphocytes [13]. The levels of serum G-, M- and A- immunoglobulins were estimated based on monospecific antiserums [16]. The proliferation activities of T- and B-lymphocytes were estimated with the ballast transformation reactions of lymphocytes (BTLR) with phytohemaglutinin (PHA), concovallin A (Con A), pokeweed mitogen (PM) based on incorporation of tritiated thymidine (^{3}H thymidine) [8]. Moreover, the functional activity of T-lymphocytes was examined in the delayed-type skin hypersensitivity reaction (DTH) with autologous modified lymphocytes [1]. Diagnostic tumor growth tests (TUR-tests) were completed in the modified hemagglutination reaction (immunomodification of ESR) using an antiidiopathic and antiembryonic serum [2]. The concentrations of carcinofetal antigen (CFA) in blood serum were determined with a radioimmune assay method with a RIO-REA [CFA]- ^{125}I-M set (Institute of Bioorganic Chemistry (IBOKH), Minsk, Belarus). The diagnostic significance of different clinical signs and methods of LC diagnostics was assessed based on their sensitivity and specificity [6]. The reference group was composed of 40 healthy volunteer donors aged 30 to 55. Statistical analysis was based on the Student's t-test.

Findings and discussion

THE CLINICAL SIGNS OF ILLNESSES DO HAVE A CERTAIN PRACTICAL VALUE FOR DIAGNOSTICS OF LUNG CANCERS. FOR THE CENTRAL CANCER SUCH CLINICAL SIGNS INCLUDE COUGHING, BLOOD SPITTING, CHEST PAINS, DYSPNEA, ELEVATED BODY TEMPERATURES. AS TO PERIPHERAL CANCERS, THEY DO NOT SHOW ANY SYMPTOMS FOR A LONG TIME, AND CLINICAL SIGNS ARE MUCH LESS PRONOUNCED. COUGHING, THE MOST FREQUENT LC SYMPTOM, WAS OBSERVED FOR 69.5 % OF ALL PATIENTS, AND WAS TWO TIMES MORE FREQUENT AT CENTRAL CANCERS. DURING EXAMINATIONS 35 (66 %) OF CNLD AND 3

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(18.8 %) OF BLT PATIENTS HAD COMPLAINTS OF COUGHING. BLOOD SPITTING, THE MOST CHARACTERISTIC SIGN OF MALIGNANT LUNG DAMAGE WAS FOUND IN 21 (19.3 %) AND 7 (9 %) CASES FOR THE CENTRAL AND PERIPHERAL LUNG CANCERS, RESPECTIVELY. THIS SIGN, HOWEVER, WAS FOUND ONLY FOR 3 CNLD PATIENTS; NO CASES OF BLOOD SPITTING WERE FOUND FOR THE BLT PATIENTS. CHEST PAINS ON THE DAMAGED SIDE WERE OBSERVED FOR 72 (38.5 %) OF THE LC PATIENTS IN TOTAL; 4 PATIENTS PRESENTED THEIR PROBLEMS OF CHEST PAINS ON THE OPPOSITE SIDE OF THEIR TUMORS. FOR THE BLT AND CNLD PATIENTS CHEST PAINS WERE OBSERVED IN 2 AND 9 CASES, RESPECTIVELY.

ELEVATED BODY TEMPERATURES (FEVERS) WERE REGISTERED FOR 57 (30.4 %) OF LC PATIENTS AND 16 (30.2 %) OF CNLD PATIENTS. NORMAL BODY TEMPERATURE AND LOW GRADE FEVERS WERE FOUND IN 14 AND 2 BLT PATIENTS, RESPECTIVELY. SUCH SYMPTOMS AS HUSKY VOICE AND VOCAL CORD PARESES WERE FOUND ONLY IN 5 OF THE CENTRAL CANCER

PATIENTS AT METASTATIC LESIONS OF LYMPHATIC NODES OF MEDIASTINAL SEPTUMS WITH RECURRENT NERVE INVOLVEMENT.

THE CLINICAL SIGNS OF LUNG DISORDERS ARE RATHER SIMILAR AND LOW SENSITIVE, AND THEIR APPLICATION FOR DIAGNOSTIC PURPOSES IS RESTRICTED. MORE THAN ONE THIRD OF ALL PERIPHERAL LC PATIENTS AND MORE THAN A HALF OF BLT PATIENTS HAD NO COMPLAINTS, AND CHANGES IN THEIR LUNGS WERE FOUND AT THE PREVENTIVE X-RAY EXAMINATIONS.

THE PARANEOPLASTIC SYNDROMES, KNOWN TO BE THE NONSPECIFIC TUMOR MARKERS ARE OF SPECIAL INTEREST FOR THE LC DIAGNOSES [12]. OUR DATA REVEALED 77 DIFFERENT PARANEOPLASTIC SYNDROMES OF MALIGNANT TUMORS IN 50 LC PATIENTS (26.7 % OF THE TOTAL) (SEE TABLE 1). MOREOVER, 2 SYNDROMES OR MORE WERE FOUND IN 21 PATIENTS. THE DIAGNOSTIC SIGNIFICANCE OF SUCH MARKERS IS NOT EQUAL. TO ILLUSTRATE, AS THE PARANEOPLASTIC MARKERS WE CLASSIFIED FEVERS RESISTANT TO ANTI-INFLAMMATORY THERAPY, AND ALSO ANEMIA IN THE ABSENCE OF HEMOLYSIS AND BLEEDING. OF THE 77 PARANEOPLASTIC MANIFESTATIONS TOTAL 60 (78 %) EXISTED FROM THE DATE OF THEIR INITIATION TO THAT OF THE LC DIAGNOSIS FOR A FEW DAYS, WEEKS, MONTHS, AND EVEN YEARS. BECAUSE OF THIS, THE PARANEOPLASTIC SYNDROMES MAY BE USED AS THE CLINICAL MARKERS FOR EARLY DETECTION OF MALIGNANT LUNG TUMORS.

TABLE 1. PARANEOPLASTIC MANIFESTATIONS IN LUNG CANCER (LC) PATIENTS

Paraneoblastic sign	Occurrence frequency	
	Absolute	%
Skin itch	5	2.7
Fever	14	7.5
Anemia	21	11.2
"Drumstick" syndrome	23	12.3
Hyperthrophic osteoarthropathy	3	1.6
Rheumatic arthritis	5	2.7
Thrombophlebitis	3	1.6
Itsenko-Cushing syndrome	1	0.5
Gynecomastia	1	0.5
Acanthosis nigricans	1	0.5
TOTAL:	77	41.1

A total of 159 patients were diagnosed of lung cancers with the X-ray method. At the same time, however, 8 CNLD and 7 BLT patients were found suspicious for malignant pulmonary tumors after X-ray examinations. As a result, the sensitivity of this method reached 85 % at 78.3 % specificity. Accuracy of cytology examinations of sputum was equal to 49 % and 18 % for the central and peripheral cancers, respectively. Hyperdiagnostics for the group of CNLD patients was observed in 2 cases.

Endoscopy examinations were completed with a Japan-produced Type-20 BF fiber optic bronchoscope on 170 patients under local anesthesia. Direct bronchoscopy signs were observed in 89 patients having LCs in their exophitic forms; the indirect signs were found in 17 patients suffering from the central lung cancer in its peribronchial form. Sensitivity of this method was equal to 97.2 %. For a group of peripheral cancer patients the direct and indirect

ENDOSCOPY SIGNS WERE FOUND IN 2 AND 7 CASES, RESPECTIVELY, AND TOTALED 47.4 % OF 19 PERSONS EXAMINED WITH SUCH A METHOD. FOUR OF OUR 42 CNLD PATIENTS SHOWED INDIRECT BRONCHOSCOPIC SIGNS OF PERIBRONCHIAL CANCERS. THE SPECIFICITY OF ENDOBRONCHIAL METHOD WAS EQUAL TO 90.5 %.

AS TO THE TRANSTHORACIC PUNCTURES, THEY WERE ACCURATE IN 33 OF 40 PERIPHERAL LC PATIENTS TOTAL, AND AT 82.5 % LEVEL OF SENSITIVITY. NO CASES OF HYPERDIAGNOSTICS IN THE BLT (7) AND CNLD (9) PATIENTS WERE FOUND, AND SPECIFICITY IN THIS CONTEXT REACHED 100 %. GENERAL MORPHOLOGY VERIFICATION WAS OBTAINED FOR 92 (84.4 %) AND 61 (78.2 %) OF LC PATIENTS IN THE CENTRAL AND PERIPHERAL FORMS, RESPECTIVELY.

ACTIVE STUDIES ARE NOW IN PROGRESS THE FIELD OF IMMUNE DIAGNOSTICS OF MALIGNANT NEOPLASMS. OUR DATA REVEALED THAT AVERAGE CONCENTRATIONS OF LYMPHOCYTES IN THE LC PATIENTS WERE NOT MUCH DIFFERENT FROM THOSE FOR BLT OR CNLD CASES, AND ALSO THOSE FOR HEALTHY HUMANS (TABLE 2). A TREND WAS NOTED TO HIGHER CONCENTRATIONS OF B-LYMPHOCYTES IN THE LC AND CNLD PATIENTS AS COMPARED TO HEALTHY INDIVIDUALS AND BLT PATIENTS. ANY RELIABLE CHANGES IN THE LEVELS OF THE MAJOR CATEGORIES OF SERUM IMMUNOGLOBILINS WERE NOT FOUND. IT SHOULD BE EMPHASIZED THAT FIRST-LEVEL IMMUNOLOGY INDICES ARE CHARACTERISTIC OF GREAT VARIATIONS IN AVERAGE AND INDIVIDUAL PARAMETERS; THE LATTER FACT MAKES DIFFICULT THEIR APPLICATION FOR DIFFERENTIAL DIAGNOSTIC PURPOSES.

ANALYTICAL CONSIDERATION OF MITOGEN-STIMULATED BLAST TRANSFORMATION DATA HAS SHOWN THAT PROLIFERATION LYMPHOCYTE RESPONSES TO ALL THE APPLIED MITOGENS FOR THE LC PATIENTS WERE LOWER THAN THOSE FOR THE REFERENCE GROUP. THE MOST

SIGNIFICANT DIFFERENCE WAS FOUND FOR THE RESPONSE TO POKEWEED MITOGEN (PM); THE STIMULATION INDICES FOR DIFFERENT STAGES OF THE DISEASE WERE NEARLY EQUAL (STAGES I-II - 14.0 ± 1.9; STAGES III-IV - 14.4 ± 1.7; REFERENCE - 39.1 ± 3.2). ON ADDITION OF PHA AND CON A THE PROLIFERATION LEVELS DECREASED WITH PROGRESS OF THE DISEASE; A SIGNIFICANT INHIBITION OF IMMUNOLABEL INCORPORATION AS COMPARED TO THE REFERENCE GROUP WAS FOUND FOR THE STAGE III-IV PATIENTS ($P < 0.01$).

THE CONCENTRATIONS OF CARCINOFETAL ANTIGEN (CFA) EXCEEDED THE REFERENCE STANDARD (7.3 ± 1.85 NG/ML) IN 95 LC; 3 BLT; AND 23 CNLD PATIENTS, AND ALSO IN 4 HEALTHY INDIVIDUALS. THE SENSITIVITY AT DETERMINATION OF THE ANTIGEN WAS EQUAL TO 50.8 % AT 62.3 % SPECIFICITY.

TABLE 2. IMMUNOLOGY PARAMETERS IN LUNG DISEASE PATIENTS (M ± M)

		DIAGNOSIS					
PARAMETER	HEALTHY	LUNG CANCER (LC)				BLT	CNLD
	PERSONS	STAGE I	STAGE II	STAGE III	STAGE IV	(N = 16)	(N = 53)
	(N = 40)	(N = 37)	(N = 54)	(N = 68)	(N = 28)		
LYMPHOCYTES:							
%	29.2 ± 1.12	29.3 ± 3.84	26.1 ± 2.81	24.7 ± 3.51	25.4 ± 1.95	30.2 ± 2.01	26.8 ± 2.15
ABSOLUTE VALUE	1947 ± 247.5	1850 ± 278.5	1783 ± 273.5	1921 ± 217.6	1657 ± 248.9	2058 ± 156.4	1834 ± 233.6
T-LYMPHOCYTES							
%	61.2 ± 1.61	58.6 ± 2.31	57.7 ± 3.43	54.7 ± 3.54	56.4 ± 4.75	59.3 ± 3.96	55.7 ± 4.39
ABSOLUTE VALUE	1187 ± 56.3	1034 ± 140.8	1012 ± 44.3 *	1045 ± 76.8	976 ± 63.5 *	1214 ± 98.3	1019 ± 96.7
B-LYMPHOCYTES							
%	14.2 ± 0.45	16.5 ± 1.83	15.7 ± 0.81	17.0 ± 1.59	16.8 ± 2.38	14.9 ± 0.61	16.3 ± 0.39
ABSOLUTE VALUE	275 ± 14.3	293 ± 31.8	256 ± 26.5	326 ± 48.4	311 ± 45.4	306 ± 32.5	293 ± 21.6

IgG (g/l)	13.56 ± 0.45	14.26 ± 0.47	13.48 ± 0.69	13.14 ± 0.61	13.26 ± 0.68	12.94 ± 0.41	12.73 ± 0.65
IgA (g/l)	2.15 ± 0.19	2.19 ± 0.18	2.13 ± 0.21	2.10 ± 0.19	1.98 ± 0.16	2.11 ± 0.14	1.95 ± 0.20
IgM (g/l)	1.30 ± 0.09	1.45 ± 0.11	1.38 ± 0.20	1.46 ± 0.16	1.29 ± 0.16	1.31 ± 0.17	1.54 ± 0.14
Note: * - Reliable difference as compared to the reference group							

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Based on examinations of delayed-type skin hypersensitivity reaction (DTH) with autologous modified lymphocytes it was found that the occurrence frequency of positive reactions for the BLT patients was equal to 6.3 % as compared to the CLDT patients (9.4 %) and healthy individuals (5 %). As to the Stage I-III lung cancer patients, the reaction was positive in 91.2 % of all cases; for Stage IV patients it was positive in 75.0 % of cases. Sensitivity of skin tests was equal to 88.8 % at 91.3 % specificity. It should be noted that the method was found to be highly sensitive at the Stage I of lung cancers (at 86.5 %), which is important for early diagnostics of the disease.

Completion of TUR-tests for tumor growth showed sensibility of this method in the LC patients at 89 % level, and specificity at 86 %. The TUR-test is a rather technically simple procedure, and it may be recommended for screen testing in outpatient clinics at preventive examinations.

Combined application of immunology testing jointly with the pther procedures turned out to be more informative the most common X-ray, endoscopy, and morphological methods of LC diagnostics (Table 3).

THUS, BASED ON THE COMPLETED ANALYSIS WE HAVE FOUND A NUMBER OF SPECIFIC FEATURES IN THE CLINICAL BEHAVIOR OF LUNG CANCERS, WHICH EXHIBIT POLYMORPHIC PATTERNS OF THEIR CLINICAL, LABORATORY, RADIOLOGICAL, AND ENDOSCOPY SIGNS. NOT INFREQUENT ARE THE CASES OF ASYMPTOMATIC OR LOW SUSPECTED CLINICAL DISEASE COURSES WITHOUT ANY DISTURBANCES OF GENERAL CONDITION OF PATIENTS OR CHANGES IN THE PERIPHERAL BLOOD AND BODY TEMPERATURE. NOT INFREQUENT ARE THE OBSERVATIONS WHERE THE CLINICAL X-RAY PATTERNS OF LUNG TUMORS ARE SIMILAR TO CHRONIC LUNG DISORDERS. THE ABOVE PROBLEMS MAKE ACCURATE DIAGNOSTICS DIFFICULT AND REQUIRE DEVELOPMENT OF SPECIAL EXAMINATION PROCEDURES FOR TIMELY DETECTION OF THIS FORM OF CANCER. INCORPORATION OF THE IMMUNOLOGY TESTING INTO COMBINED DIAGNOSTICS OF RESPIRATORY ORGANS' DISEASES WILL IMPROVE THE ACCURACY OF LC DIAGNOSES.

TABLE 3. OCCURRENCE FREQUENCIES FOR ACCURATE DIAGNOSES IN LUNG DISEASE PATIENTS VS. DIAGNOSTIC PROCEDURES

	DIAGNOSTIC PROCEDURE							
DIAGNOSIS :	X-RAY		ENDOSCOPY		MORPHOLOGICAL		COMBINED	
	A	B	A	B	A	B	A	B
LC	187	159 (85)	128	115 (89.8)	187	153 (81.8)	187	181 (96.8)
BLT	16	9 (56.3)	-	- -	16	9 (56.3)	16	15 (93.8)
CLDT	53	45 (84.9)	42	38 (90.5)	-	- -	53	51 (96.2)

NOTE: A – NUMBER OF PATIENTS; B – NUMBER OF ACCURATE DIAGNOSES; THE PARAMETER IN PER CENT IS SHOWN IN PARENTHESES

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